

## EDITORIAL

# The declining prevalence of ST elevation myocardial infarction in patients presenting with acute coronary syndromes

N S Kleiman, H D White

The management of patients with acute coronary syndromes may be about to undergo a dramatic change

Heart 2005;91:1121-1123. doi: 10.1136/hrt.2004.056085

It is well recognised that mortality from coronary heart disease has been declining in the developed world for the past three decades.<sup>1</sup> Nearly as well recognised is the change that has occurred in the presenting features of patients with acute coronary syndromes (ACS), from a predominance of ST elevation myocardial infarction (MI) to a scenario in which ST elevation is typically absent. Several registries have reported notable declines in the incidence of ST elevation MI.<sup>2-3</sup> Accompanying these trends, the overall proportion of admissions for chest pain caused by MI is also declining, while several sources have indicated that the incidence of unstable angina is increasing.<sup>4</sup> These findings have important implications for clinicians and researchers, as well as for those who allocate healthcare resources.

Traditional explanations for this phenomenon have focused on advances in primary and secondary prevention, such as treatment with aspirin, statins, and appropriate revascularisation. In addition, more widespread measurement of biomarkers of myonecrosis has increased the rate of diagnosis of MI in patients with non-specific electrocardiographic features. While there is little question that such strategies have recently been utilised more aggressively than in the past, findings in the current issue of *Heart* suggest that advances in diagnosis and treatment may not be the only explanations for the declining prevalence of ST elevation MI in patients presenting with ACS. Reporting for the EuroHeart investigators, Rosengren and colleagues found that several simply detected clinical risk factors were powerful predictors of the presence of ST elevation at the time of presentation with ACS.<sup>5</sup>

## CIGARETTE SMOKERS

The findings are taken from a very broad based registry of 10 253 patients with a discharge diagnosis of ACS, treated in 103 hospitals in 25 countries in Europe and the Mediterranean basin. Only 43% of patients had ST elevation; among these patients, MI was detected in 87%, compared with 33% of patients without ST elevation. Rosengren *et al* found that cigarette smokers were more likely to present with ST

elevation ACS, while patients with hypertension and/or obesity were more likely to present with non-ST elevation ACS.<sup>5</sup> Although statin use did not predict the modality of presentation, recent data (obtained since the completion of this study) would suggest that low dose statin treatment may not be sufficient to prevent cardiovascular events.<sup>6</sup> Unfortunately, the EuroHeart report does not mention the doses of the various statins used in the study.

As is true of many clinical findings, the mechanisms postulated to explain the EuroHeart observations are tenuous. ST elevation is conventionally thought of as signifying transmural ischaemia in response to fissuring or rupture of an atheromatous plaque with total and prolonged occlusion of a major coronary artery, while ST depression is usually associated with plaque disruption and incomplete coronary occlusion, or occlusion of either a small branch artery or the distal left circumflex artery. Cigarette smoking increases platelet aggregability and is a prothrombotic stimulus.<sup>7</sup> Reports from the early placebo controlled trials of fibrinolysis indicated that among patients with acute MI, cigarette smoking was associated with a favourable prognosis after fibrinolysis, suggesting that smokers' acute coronary events were more likely to be caused by acute thrombosis rather than fixed atherosclerotic narrowings.<sup>8-9</sup> Thus cigarette smoking may increase the risk of total occlusion of a culprit vessel in patients who might otherwise have less underlying atherosclerosis.

## OTHER RISK FACTORS

The pathophysiological roles of the other risk factors identified in this study are less clear. Hypertension is recognised as a risk factor for atherosclerotic events, and may cause fixed atherosclerosis rather than acute thrombosis. The consequences of secondary left ventricular hypertrophy and its effects on the ST segment in this setting are also likely to be important. The role of obesity in predisposing patients to non-ST elevation ACS is unclear, but may relate to associated risk factors of dyslipidaemia, hypertension, and insulin resistance, particularly in patients with truncal obesity, which is not discussed in the report. Recent findings have

**Abbreviations:** ACS, acute coronary syndromes; BMIPP,  $\beta$ -methyl iodophenyl pentadecanoic acid; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction

See end of article for authors' affiliations

Correspondence to: Professor Harvey White, Cardiology Department, Auckland City Hospital, Private Bag 92024, Auckland 1030, New Zealand; harveyw@adhb.govt.nz

suggested that inflammatory cytokines are upregulated in obese patients.<sup>10</sup> Left ventricular hypertrophy in obese patients may also influence their electrocardiographic response to ischaemia.

However, these findings may also be explained by demographic differences in the patient population. It has been recognised for well over a decade that patients with ST elevation ACS are likely to be younger and to have fewer diseased coronary arteries than their counterparts with non-ST elevation ACS. Obesity and hypertension largely correlate with the ageing process (as the authors can attest from personal experience), while cigarette smoking is more common in younger patients, perhaps partly as a result of social conventions, and partly as a result of (un)natural selection. As the population ages, pursues excessive and unhealthy eating habits, and ceases smoking, it is likely that the presenting characteristics of patients with ACS will continue to change. With the added impact of more aggressive aspirin use and appropriate dosing of statins, it is likely that the trends already documented will accelerate.

## IMPLICATIONS

What are the implications of these findings? Clearly, the intent of smoking cessation, weight reduction, and hypertension control is to prevent clinical events rather than to modify the ECG when an event does occur. Rather than providing a rationale for risk factor modification, the EuroHeart report should be regarded as a barometer. The features identified as important predictors of non-ST elevation ACS are increasing in frequency and will probably continue to do so, while the resources marshalled to decrease cigarette smoking are also showing signs of efficacy.<sup>11</sup> Recent legislative changes in various countries to ban smoking in workplaces, bars, and restaurants may tip the societal balance of smoking tolerance towards non-acceptance, and smoking rates in the general population may consequently decline to less than 20%. The availability of endocannabinoid receptor antagonists such as rimonabant may accentuate this trend.<sup>12</sup>

The major import of the findings by Rosengren *et al*<sup>5</sup> is that the trend in the changing presentation of ACS will continue and probably accelerate. Given the diagnostic uncertainty that often surrounds patients with non-ST elevation ACS, diagnosis is going to become more rather than less difficult. For example, in the thrombolysis in myocardial infarction (TIMI)-IIIA trial of patients presenting with rest angina and either ST deviation or known pre-existing coronary artery disease, angiography (which was protocol mandated in all patients) revealed that >20% had normal or minimally narrowed coronary arteries.<sup>13</sup> The diagnosis and optimal treatment of patients with ST elevation ACS is relatively straightforward. Reperfusion therapy, whether by fibrinolysis or by direct percutaneous coronary intervention (PCI), is established as the most important treatment modality. In the USA and Europe, a groundswell is forming to hasten the delivery of patients to centres capable of performing emergency PCI. At least one study has been cited as demonstrating that small hospitals that do not perform PCI routinely can and should perform direct PCI for acute ST elevation infarction.<sup>14</sup> However, if the current observations are representative of the larger population, this strategy may not represent the most effective long term allocation of resources. While two recent reports have suggested that very early angiography may be more beneficial than conservative treatment in patients without ST elevation,<sup>15 16</sup> they are based on small trials with insufficient statistical power to provide reliable point estimates of the benefit of this treatment. Thus it is by no means clear that establishment of early angiography centres will be the best way to serve the needs of the future patient population.

## INCREASING NUMBER OF PATIENTS WITH ACS

What is becoming clear is that future resources will need to be shifted to manage the increasing volume of patients with non-ST elevation ACS. Each year, more than 1.5 million individuals with ACS are admitted to hospitals in the USA, and perhaps 4 million more worldwide. What is needed? We believe that the early phases of management will need to be directed towards accurate diagnosis and risk stratification. The ECG is a wonderful tool, which has been in use for nearly a century—and every year new papers are published that further expand its utility. For example, indications for such life saving treatments as defibrillator implantation and biventricular pacing are in part based on electrocardiographic findings. However, as far as the use of electrocardiography for ACS triage is concerned, very little progress has been made beyond determining whether or not ST segments are elevated.

A variety of risk scores using simple criteria have been developed from clinical trials and registries.<sup>17–19</sup> Although useful to predict responses to certain treatments<sup>17 20 21</sup> and to provide broad perspectives on likely outcomes, these scores rely heavily on “biomarkers” such as troponins or creatine kinase and its isoforms. As far as has been shown, detection of these markers requires myocyte necrosis, disruption of the cell membrane, and release of complex proteins into the circulation. Consequently their utility in the early hours after presentation is limited. “Multimarker” approaches have refined the predictive value of these indices,<sup>22</sup> but they are still tied to the detection of cell death. Disruption of a “vulnerable plaque” is considered to be the pathophysiological hallmark of ACS, although in some patients, thrombogenicity of the blood (“vulnerable blood”) is also implicated. Alternative and novel approaches are desperately needed. If we are to have an impact on the early diagnosis of ACS, attention will need to be focused on detecting plaque disruption and myocardial ischaemia as readily as we can now detect infarction. The magnitude of this challenge should not be underestimated. A disrupted coronary plaque is roughly the size of a match head. Any markers released at the site of arterial injury are subject to immediate dilution in a 5 litre pool of blood, making detection difficult. Measurement of more generalised markers of inflammation is obviously limited by the inability to distinguish intracoronary processes from inflammation elsewhere in the body, and may even be influenced by other cardiac processes such as heart failure.

## ALTERNATIVE APPROACHES

Alternative approaches now under investigation include an aggressive approach to imaging. High resolution computed tomographic scanning can now be performed within a matter of minutes, and preliminary results suggest that its specificity for detection (or exclusion) of coronary stenoses is high. Scintigraphic studies using radiolabelled anti-annexin antibodies can detect apoptotic macrophages in recently disrupted plaques.<sup>23 24</sup> When combined with high resolution gamma detection, such approaches also offer the opportunity for non-invasive detection of thrombogenic intracoronary plaques. Another imaging development currently in early clinical trials involves technetium labelled fatty acids.<sup>25</sup> An important problem frequently encountered when taking a history from a patient with ACS is that the index episode of angina has subsided by the time an ECG is obtained. In animal models, use of radiolabelled  $\beta$ -methyl iodophenyl pentadecanoic acid (BMIPP) allows detection of myocardium that has been ischaemic within the past 24–36 hours.<sup>26</sup> It is not difficult to imagine how these diagnostic modalities could be combined to yield estimates of the extent and location of myocardium at risk. Combination of such novel

approaches with multimarker assessment, perhaps using computerised algorithms, is likely to provide both an extremely powerful predictor of risk and an indicator of therapeutic alternatives. While some of these concepts may seem unreal, they are already in, or very close to, clinical evaluation. Considering these possibilities and the implication of the EuroHeart findings, we believe that the management of patients with ACS is about to change dramatically.

#### Authors' affiliations

**N S Kleiman**, The Methodist DeBakey Heart Center, Section of Cardiology, Baylor College of Medicine, Houston, Texas, USA  
**H D White**, Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand

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